의학박사 학위논문

Hypertension Risk with Abacavir Use among HIV-Infected Individuals : A Nationwide Cohort study

HIV 감염인에서 아바카비어 약제로 인한 고혈압 발생위험 평가: 코호트연구

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Abstract

Background: While a link between abacavir and CVD risk is suggested, an association between abacavir and hypertension remains unclear.

Purpose: To validate the use of claims database in research of HIV-infected individuals, and evaluate the incidence and risk of hypertension induced by abacavir among HIV–infected individuals.

Materials and Methods: We constructed a nationwide cohort of HIV-infected individuals using the Health Insurance Review and Assessment Service (HIRA) database of the National Health Insurance System (NHIS) from the period of 2007-2016, and compared the numbers of individuals with the official reports of the government. From 6093 HIV-infected individuals on their initial ART, 1,234 who had used abacavir or non-abacavir ART without switch were were selected after propensity score matching. The use of ART was treated as a time-varying covariate measured as a daily unit. Incidence rate of hypertension was calculated, and Cox proportional hazard models were used to estimate adjusted hazard ratios (HRs) with their 95% confidence interval (CI) of incident hypertension overall and among subgroups.

Results: The cohort from HIRA database showed similar numbers of individuals with the ones detected by the government. Among the total 6,093 HIV-infected individuals, incidence rates of hypertension were 4.6

and 3.6 per 100 person-years for abacavir and non-abacavir ART users, respectively. The population attributable fraction of abacavir use on hypertension was 12%. Among the matched 1,234 subjects, abacavir exposure elevated the risk of hypertension among overall study population. However, those aged over 30's, with psychiatric disorders, and diagnosed after the year 2013 were at higher risk of hypertension induced by abacavir.

Conclusion: We constructed a database that can be used as a source of HIV epidemiology studies in the future. Those diagnosed after the year 2013 may warrant additional concern for hypertension in patients treated with abacavir.

Keywords : hypertension; abacavir; HIV; antiretroviral therapy; epidemiology

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1. Introduction

1.1 Background

Hypertension is the most important risk factor for a variety of premature cardiovascular diseases (CVDs). Research has indicated that HIV infection increases blood pressure[1] and that traditional CVD risk factors, such as hypertension, contributes additional risk, independent of and in addition to that contributed by HIV infection.[2] While exposure to antiretroviral treatment (ART) has been reported to increase blood pressure with an odds ratio of 1.68, there is scarce data on whether a specific ART increases the risk.[3]

Abacavir, a first-line ART agent, has been on the market since 1998. In 2008, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study reported an association between recent abacavir exposure and an increased rate of myocardial infarction.[4] Nevertheless, studies have yet to confirm how and whether or not abacavir elevates CVD risk[5-8]: it is necessary to confirm the long-term safety of abacavir use because, ultimately, people living with HIV (PLWH) will be on ART for decades. While one study has shown that, among several ARTs, only patients using abacavir exhibit a slightly higher risk of hypertension,[9] no study has conducted a survival analysis of the hypertension risk associated with abacavir use in initial ART among PLWH over an extended follow-up duration.

While the database of nationwide HIV-infected individuals is managed only by the government, Korea Center for Disease Control and Prevention (KCDC), there is no history of using the database as a source of any epidemiological studies. However, there is a fully covered health insurance of all national population in South Korea, of which has many potential is its use in epidemiological studies. Since it is particularly difficult to recruit HIV-infected individuals regarding prejudice among the infected, creating a

database for the source of HIV researches is more than necessary.

1.2 Objectives

In order to assess the possibility and validity of using claims database as a source for HIV epidemiology studies, we constructed a nationwide cohort (from 2008 to 2016) of HIV-infected individuals using the HIRA database from 2007-2016. Also, In order to evaluate the risk of hypertension with abacavir use in comparison to non-abacavir ART, we analyzed the cohort considering drug exposure as a time-varying covariate measured on a daily basis.

2. Materials and Methods

2.1 Data source

The National Health Insurance System (NHIS) in the Republic of Korea (ROK) began in 1963 and has been the single insurer of the entire population, currently about 52 million, since 2000. This study used data from the Health Insurance Review and Assessment Service (HIRA) database, which includes the claims data of the NHIS and National Medical Aid (NMA), which cover 97% and 3% of the entire population, respectively. The HIRA database includes all information regarding patient diagnosis (using the International Statistical Classification of Diseases and Related Health Problems 10thr evision [ICD-10]codes),names of procedures, drug prescriptions, health insurance status (NHIS or NMA), types of medical institution visited, and health care costs.[10] The HIRA database has been used in other research regarding hypertension[11,12] and in a HIV adherence study.[13] This database contains comprehensive data on the use of ART because, since 1989, all healthcare claims, including ART, are fully reimbursed when the condition

claimed for their use is relevant to HIV infection.

2.2 Study population

We used the 2007–2016 HIRA databases to establish a cohort of incident HIV-infected individuals on initial ART (Figure 1). PLWH who received ART treatment at least once were defined as HIV-infected individuals, with an exclusion of those who were likely to have received ART for other preventive care and with a minimum of one year as the window period for defining incident cases. Eventually, 9283 incident HIV-infected individuals with initial ART prescription from 2008-2016 were recruited. After excluding 2790 (30.0%) individuals with prevalent hypertension at cohort entry, 6493 were included as the final study population. A similar method of selecting HIV-infected individuals was used in another study.[13] The numbers of prevalent or incident HIV-infected individuals on ART were compared to the official reports from the government.

2.3 Assessment of exposure and outcome definitions

Drug exposure was categorized into two groups (abacavir and non-abacavir ART), and the switch between the two were applied as a time-varying covariate on a daily basis. That is, the kind of ART (abacavir or non-abacavir ART) a participant received was assessed on a daily basis. When abacavir and non-abacavir ART were both prescribed for the same day, it was counted as abacavir exposure. The day of initial ART was the cohort entry day, and patients were followed until either incident hypertension diagnosis or the last day of study period (December 31, 2016). Hypertension was defined as at least two claims and also during more than 6 months of antihypertensive

treatment prescriptions. The choice for proper definition of outcome was explored in many ways in the sensitivity analysis.

2.4 Potential confounders

All comorbidities and co-medications were defined based on information prior to cohort entry. The following confounders related to the probability of prescribing abacavir instead of tenofovir were adjusted for: acute kidney failure, end stage renal disease (ESRD), osteoporosis, and history of switching between abacavir and non-abacavir ART. Acute kidney failure comprised kidney ischemia or infection, as well as temporary proteinuria, while ESRD included chronic kidney disease and dialysis or transplant related status. Factors related to hypertension, such as alcohol drinking, diabetes, dyslipidemia, atherosclerosis, history of medications, such as antidiabetic agent or statins, and prior history of exposure to protein inhibitors (PIs) or nucleoside analogue reverse transcriptase inhibitors (NRTIs) known to increase CVD risk were also adjusted for. An individual with AIDS was defined as one who received at least one diagnosis of an AIDS-defining illness, defined by the CDC.[16] Requiring prophylactic antibiotics included having been prescribed a prophylactic dose of oral trimethoprim-sulfamethoxazole (80 mg/400 mg: 1 tablet daily, 1 tablet twice daily, or 2 tablets daily) or oral dapsone (100 mg daily or 200 mg weekly). We assumed that individuals requiring prophylactic antibiotics had a CD4+ T-cell count <200 cells/μL, since PLWH must meet strict indication criteria that are supervised and supported by the government. PIs with known CVD risk included lopinavir, indinavir, and darunavir (including ritonavir boosted products)[17]; NRTIs with known CVD risk included didanosine, stavudine, and zidovudine.[4,18] Adherence was examined using the medication possession ratio (MPR), calculated as the sum of days of treatment supplied for all ART prescriptions filled, from the first

ART fill date (the cohort entry date) until December 31, 2016, divided by the number of days in that same time period. NMA usage was considered a proxy for low socioeconomic status since they are considered to be the financially lowest 3% of the national population. Visiting medical institutions in metropolitan cities reflects better accessibility to healthcare, and the level of the institution reflects the level of medical care provided.

2.5 Statistical analysis

The numbers of prevalent or incident HIV-infected individuals on ART were compared to the official reports from the government to evaluate the validity of cohort individuals. Demographic and clinical characteristics of patients with and without abacavir exposure were compared using Pearson's $\chi 2$ test for categorical variables. We calculated incidence rates of hypertension for abacavir users and non-abacavir ART users among the overall study population and among subgroups with known hypertension risk. Population attributable fraction (PAF) was calculated using the incidence rates, according to Levin's formula: PAF reflects the proportion of disease in the population that can be attributed to a particular risk factor that, if eliminated, will potentially prevent the risk.[19,20] Abacavir risk is presented in hazard ratios (HRs) and 95% confidence interval (CI) using Cox proportional hazards models adjusted for potential confounders mentioned above. An alpha of 0.05 was used for all the statistical hypothesis testing, and all statistical analyses were conducted using SAS Enterprise Guide, version 6.1 (SAS Institute, Inc., Cary, North Carolina, USA). This study was approved by the Institutional Review Board of Seoul National University College of Medicine (IRB No. E-1710-070-893), and the need for informed consent was waived by the board.

2.6 Sensitivity analysis

Two kinds of sensitivity analyses were conducted; 1) when choosing the definition of outcome after exploring the pattern of outcome occurrence, and 2) when comparing the results with matched subjects using propensity scores among those who never changed the exposure status, that is without switch. The first issue was whether or not to exclude early outcomes that occurred within 9 months after cohort entry. We compared the slope of outcome appearance using the cumulative distribution function (CDF) of follow-up days. CDF of a random variable X, evaluated at x, is the probability that X will take a value less than or equal to x.

$$Fx(x)=P(X\leq x)$$

Therefore, CDF of follow-up days shows the probability of each follow-up day to end at that day, because follow-up day ends when outcome is detected. The second issue was the range of hypertension definition. We estimated hypertension risk when it was defined as same or more than two times and more than 6months of antihypertensive treatment prescriptions. We examined the number of outcomes as follow-up days pass by and made a choice based on scientific assumption considering the mechanism of hypertension.

After exploring the results of Cox Proportional Hazard (CPH) models, we limited the subjects into those without any switch between the two groups of abacavir and non-abacavir ART (reference), and matched the two groups using propensity scores. The balance was confirmed using standardized differences, and those with <0.1 were considered as well matched as suggested by Austin. The HRs before and after two different subjects were compared and one was chosen based on adequate interpretation of the results.

3. Results

Of the 11944 nationwide HIV-infected individuals from the years 2007-2016, 6493 incident ART users without hypertension before cohort entry (initial ART) from 2008-2016 were selected as the final study participants (Figure 1).

3.1 Cohort compared to the KCDC reports

The number of prevalent HIV-infected individuals detected from the claims database was about 1,000 less than the number of cumulative number of the infected reported from the KCDC (Table 1). However, the difference showed a steady decrease each year. The number of incident HIV-infected individuals was similar with that of the KCDC reports (Table 2). Higher numbers of individuals were detected from the claims cohort in recent years.

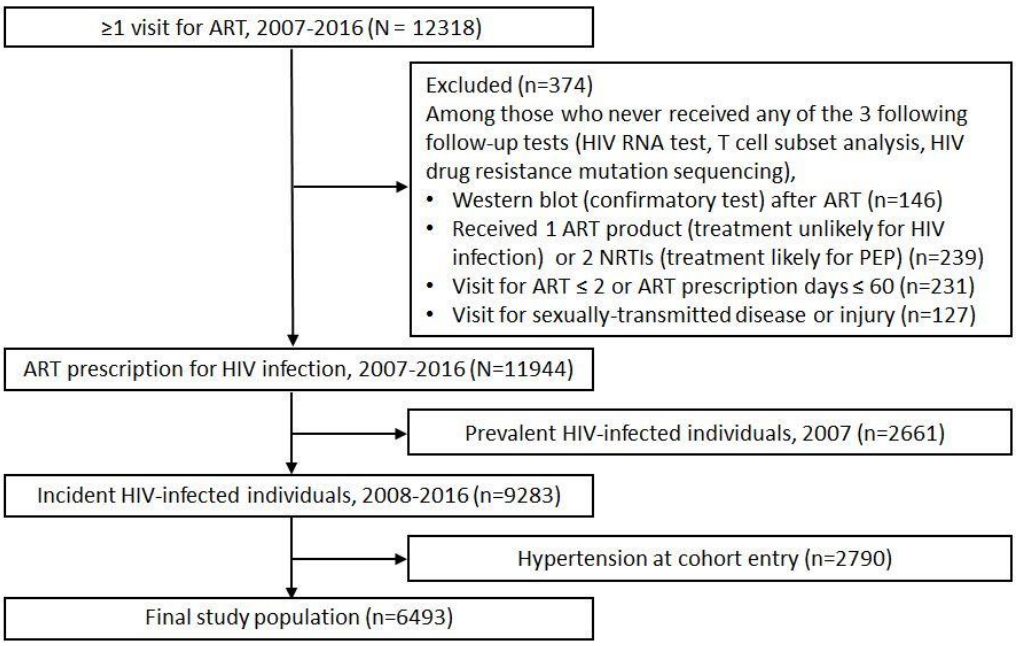


Figure 1. Selection of the study population.

ART, antiretroviral treatment; NRTI, nucleoside analogue reverse transcriptase inhibitors; PEP, post-exposure prophylaxis.

Table 1. The Number of Prevalent HIV-Infected Individuals in the Cohort Compared to the KCDC Reports

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Domestic individuals (KCDC)	4,337	5,030	5,666	6,290	7,030	7,788	8,662	9,615	10,502	11,439
Foreigners (KCDC)	648	751	822	886	957	1,042	1,143	1,253	1,387	1,524
Domestic+Foreigners (KCDC)	4,985	5,781	6,488	7,176	7,987	8,830	9,805	10,868	11,889	12,963
Cohort from the claims database	2,661	3,256	3,879	4,599	5,404	6,220	7,123	8,222	9,276	10,413
KCDC Total - Cohort	2,324	1,774	1,787	1,691	1,626	1,568	1,539	1,393	1,226	1,026
KCDC Domentic - Cohort	1,676	1,774	1,787	1,691	1,626	1,568	1,539	1,393	1,226	1,026

Table 2. The Number of Incident HIV-Infected Individuals in the Cohort Compared to the KCDC Reports

	2008	2009	2010	2011	2012	2013	2014	2015	2016
Domestic individuals (KCDC)	797	768	773	888	868	1,013	1,081	1,018	1,062
Domestic+Foreigners (KCDC)	900	839	837	959	953	1,114	1,191	1,152	1,199
Cohort from the claims database	798	781	863	963	977	1,097	1,248	1,236	1,320
Cohort - KCDC Total	-102	-58	26	4	24	-17	57	84	121

3.2 Main results of CPH models

Among the final study population, 3144 (48.4%) had been exposed to abacavir at least once, while 3349 (51.6%) had never received abacavir (Table 3). Among the total study population, 1173 (18.1%) changed at least once from abacavir to non-abacavir and 1593 (24.5%) vice versa. A total of 6493 participants were followed-up for 24072 person-years (PY), while 1599 (24.6%) developed incident hypertension during follow up from 2008 to 2016. However, after exclusion of outcomes within 9 months after the cohort entry from 646 individuals, 953 (14.7%) events occurred, resulting in incidence rates of 4.6, 3.6, and 4.0 per 100 PY among abacavir users, non-abacavir ART users, and the total HIV-infected individuals on ART, respectively (Table 4).

PAF of abacavir on hypertension was calculated as 12%. Even though abacavir seemed to increase hypertension risk before adjustment, it lost statistical significance after adjustment. However, poor ART adherence and requiring prophylactic antibiotics were statistically significant factors in the association between abacavir and hypertension (HR ranged from 1.1 to 1.9, Table 4)

Table 3. Characteristics of Incident HIV-infected Individuals on Antiretroviral Treatment during 2008-2016

	All patients		Abacavir Exposure		Non-abacavir ART Exposure		*p*-value
	N	%	N	%	N	%	
Total	6,493		3,144	48.4	3,349	51.6	
Gender							
Men	6,018	92.7	2,920	92.9	3,098	92.5	0.6
Women	475	7.3	224	7.1	251	7.5	
Age					0		
<20	206	3.2	82	2.6	124	3.7	<.0001
20-29	1,825	28.1	797	25.3	1,028	30.7	
30-39	1,888	29.1	923	29.4	965	28.8	
40-49	1,569	24.2	835	26.6	734	21.9	
≥50	1,005	15.5	507	16.1	498	14.9	
Comorbidity prior to cohort entry							
Acute kidney failure	442	6.8	211	6.7	231	6.9	0.8
AIDS defining illness	1,114	17.2	547	17.4	567	16.9	0.6
Alcohol	400	6.2	187	5.9	213	6.4	0.5
Cancer	478	7.4	236	7.5	242	7.2	0.7
COPD	1,011	15.6	469	14.9	542	16.2	0.2
Diabetes mellitus	919	14.2	412	13.1	507	15.1	0.02
Dyslipidemia	2,646	40.8	1,159	36.9	1,487	44.4	<.0001
End stage renal disease	36	0.6	26	0.8	10	0.3	0.004
Hepatitis B infection	354	5.5	143	4.5	211	6.3	0.002
Hepatitis C infection	542	8.3	255	8.1	287	8.6	0.5
Osteoporosis	338	5.2	156	5.0	182	5.4	0.4
Prior hospitalization	3,135	48.3	1,471	46.8	1,664	49.7	0.02
Psychiatric disorders	2,128	32.8	1,012	32.2	1,116	33.3	0.3
Medications prior to cohort entry							
Antidiabetic agents	184	2.8	101	3.2	83	2.5	0.09

Statins	131	2.0	66	2.1	65	1.9	0.7
ART adherence by MPR (%)					0		
95 ≤ MPR	4,414	68.0	2,087	66.4	2,327	69.5	<.0001
80 ≤ MPR < 95	681	10.5	384	12.2	297	8.9	
50 ≤ MPR < 80	569	8.8	314	10.0	255	7.6	
MPR < 50	829	12.8	359	11.4	470	14.0	
Requiring prophylactic antibiotics		38.0	1,340	42.6	1,130	33.7	<.0001
ART initiation (Year of cohort entry)							
2008	679	10.5	432	13.7	247	7.4	<.0001
2009	623	9.6	398	12.7	225	6.7	
2010	631	9.7	449	14.3	182	5.4	
2011	661	10.2	489	15.6	172	5.1	
2012	659	10.1	349	11.1	310	9.3	
2013	737	11.4	269	8.6	468	14.0	
2014	834	12.8	193	6.1	641	19.1	
2015	816	12.6	158	5.0	658	19.6	
2016	853	13.1	407	12.9	446	13.3	
Type of medical institution							
Tertiary hospitals	4,435	68.3	2,144	68.2	2,291	68.4	0.9
Others	2,058	31.7	1,000	31.8	1,058	31.6	
Region of medical institution							
Seoul (capital city)	3,275	50.4	1,674	53.2	1,601	47.8	<.0001
Metropolitan cities	1,718	26.5	831	26.4	887	26.5	
Rural	1,500	23.1	639	20.3	861	25.7	
Health Insurance status					0		
National health insurance	6,030	92.9	2,887	91.8	3,143	93.8	0.002
Medical aid	463	7.1	257	8.2	206	6.2	

ABC, abacavir; AIDS, acquired immuno-deficiency syndrome; ART, antiretroviral treatment; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MPR, medication possession ratio

Table 4. Hypertension Risk of Abacavir compared to Non-abacavir ART among Overall Study Population

	Abacavir			Non-abacavir ART			Hazard ratio (95% CI)				
	Events	PY	IR	Events	PY	IR	Unadjusted	95% CI	Adjusted[a]	95% CI	*p*-value
Overall	397	8720	4.6	556	15352	3.6	1.1	1.0-1.3	1.2	1.0-1.4	0.061
ART adherence by MPR (%)											
95 ≤ MPR	239	6050	4.0	348	10360	3.4	1(ref)		1(ref)		
80 ≤ MPR < 95	70	1353	5.2	72	2179	3.3	1.1	0.9-1.4	1.1	0.9-1.3	0.294
50 ≤ MPR < 80	56	896	6.3	78	1773	4.4	1.4*	1.2-1.7	1.4*	1.1-1.7	0.0009
MPR < 50	34	421	8.1	57	1039	5.5	1.8**	1.4-2.3	1.9**	1.5-2.4	<0.0001
Requiring prophylactic antibiotics[b]	193	3834	5.0	278	6392	4.3	1.3	1.2-1.5	1.2*	1.0-1.3	0.023

ART, antiretroviral treatment; CI, confidence interval; IR, incidence rate per 100 PY; MPR, medication possession ratio; PY, person-years

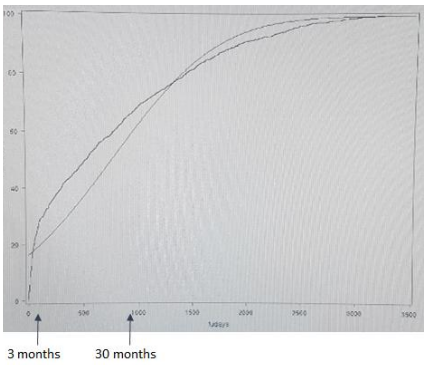
[a] Adjusted for gender, age group, antiretroviral treatment adherence, cohort entry year, CD4+ T-cell count < 200 cells/μL (yes/no), switch between abacavir and non-abacavir (yes/no), type and region of medical institution, financial status, prior history of the following: acute kidney disease, AIDS-defining illness, atherosclerosis, alcohol, cancer, COPD, diabetes, dyslipidemia, ESRD, hepatitis B infection, hepatitis C infection, osteoporosis, psychiatric disease, hospital admission, antidiabetic agent use, statin use, prescription of other ART of known cardiovascular risk, the year of ART initiation. [b] A proxy for CD4+ T-cell count < 200 cells/μL * *p*-value <0.05 ** *p*-value <0.001

3.3 Sensitivity analysis results by outcome

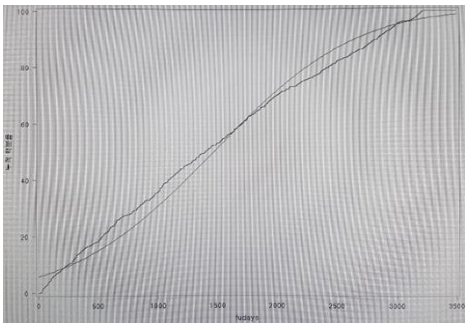
In order to explore the validity of outcome definition and whether or not to exclude early outcomes, we compared the CDF of follow-up days, examined the number of outcomes, and compared the risk of hypertension using different definition.

a. When early outcomes within 9 months of cohort entry was *not* excluded

a1. Hypertension
: 1≤diagnosis or 1≤prescription

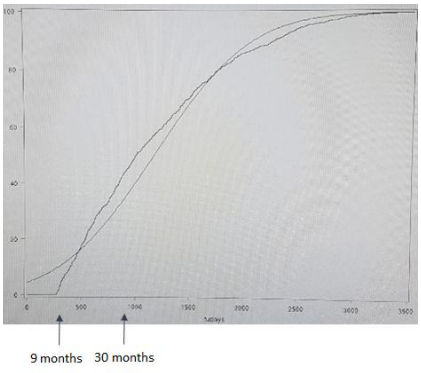


a2. Hypertension: 2≤prescriptions



b. When early outcomes within 9 months of cohort entry was excluded

b1. Hypertension
=1≤diagnosis or 1≤prescription



b2. Hypertension: 2≤prescriptions

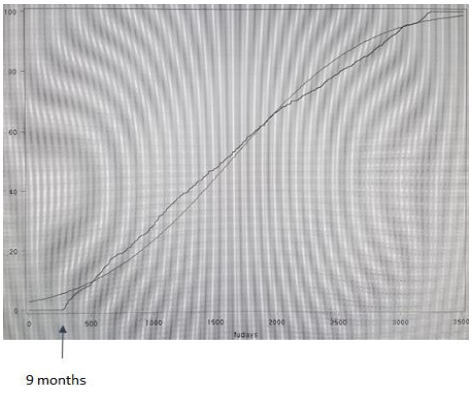
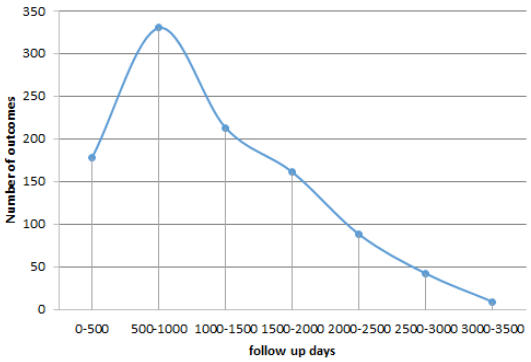


Figure 2. Comparison of cumulative distribution function of outcomes by follow-up days

a1. Hypertension
=1≤diagnosis or 1≤prescription

(When early outcomes within 9 months of cohort entry was excluded)



a2. Hypertension: 2≤prescriptions

(When early outcomes within 9 months of cohort entry was *not* excluded)

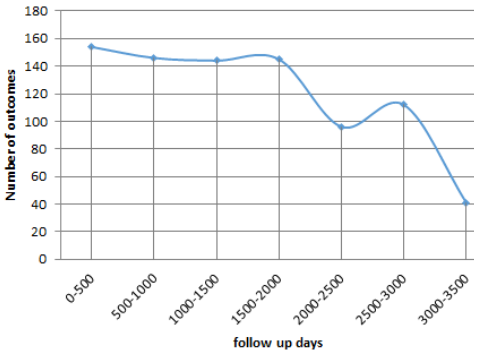


Figure 3. Comparison of number of outcomes by follow-up days

The total number of outcomes varied with different definitions of hypertension as the following: 1021 outcomes when the definition was 1≤ diagnosis or 1≤prescription of antihypertensive treatments excluding outcomes within 9 months of cohort entry, 838 outcomes when the definition was 2≤ prescriptions without excluding any outcome, and 631 outcomes when the definition was narrower as initial 2≤prescriptions within 6 months. In case of 1021 outcomes, 397 occurred during abacavir treatment, 556 during non-abacavir ART treatment, and 68 without any ART treatment.

The CDF showed two different patterns of outcome appearance: 1) early risk within 3 to 30 months of follow-up days, and 2) a steadily increasing risk (Figure 2), of which we considered that the latter is a more explainable mechanism for hypertension. The number of outcomes according to follow-up days also varied between the two kinds of definitions (Figure 3).

3.4 Sensitivity analysis results by subject

The higher risk of hypertension induced by abacavir among those with poor adherence found at the main analysis was difficult to interpretate, since it is clear that there is no preventive effect of abacavir in inducing hypertension. Therefore we limited subjects with a more strict criteria and compared the results with the main ones.

First, among the 6093 incident HIV-infected individuals, 1758 (27%) had been switched between the exposure and reference group, and 4735 (73%) had not. However, since exposure is considered as a time-varing covariate, those with switch history between the exposure and reference group may interfere propensity score matching. Therefore, we limited the study population into those without any switch and performed matching resulting in 1234 study population (Table 5).

However, after limiting study population and matching using propensity scores, higher risk of hypertension induced by abacavir among the poor adherence groups was not found (Table 6). There was marginally significant risk of hypertension induced by abacavir (HR 1.7, 1.0-3.0). Since there was a higher risk among those diagnosed with HIV infection after the year 2013, we performed survival analysis stratified by the year of diagnosis before and after 2013 (Table 7).

Table 5. Study Subjects Before and After Propensity Score Matching among HIV-Infected Individuals without Switch

	Before matching					After propensity score matching				
	Abacavir		Non-abacavirART		d	Abacavir		Non-abacavirART		d
	N	%	N	%		N	%	N	%	
Total	639		4,096			617		617		
Gender										
Men	602	0.94	3,800	0.93	0.06	580	0.94	580	0.94	0.00
Women	37	0.06	296	0.07	-0.06	37	0.06	37	0.06	0.00
Age (mean, SD)	36	11.9	37	11.6	0.03	36	11.9	37	11.6	0.03
Comorbidity prior to cohort entry										
Acute kidney failure	78	0.12	264	0.06	0.20	67	0.11	60	0.10	0.09
AIDS defining illness	99	0.15	677	0.17	-0.03	98	0.16	102	0.17	-0.02
Alcohol	44	0.07	259	0.06	0.02	41	0.07	38	0.06	0.02
Cancer	45	0.07	292	0.07	0.00	45	0.07	48	0.08	-0.02
COPD	97	0.15	643	0.16	-0.01	93	0.15	93	0.15	0.00
Diabetes mellitus	85	0.13	609	0.15	-0.05	84	0.14	90	0.15	-0.03
Dyslipidemia	307	0.48	1,723	0.42	0.12	290	0.47	283	0.46	0.02

End stage renal disease	7	0.01	17	0.00	0.08	5	0.01	5	0.01	0.00
Hepatitis B infection	24	0.04	245	0.06	-0.10	24	0.04	22	0.04	0.02
Hepatitis C infection	51	0.08	329	0.08	0.00	50	0.08	48	0.08	0.01
Osteoporosis	71	0.11	205	0.05	0.23	48	0.08	52	0.08	-0.02
Prior hospitalization	338	0.53	1,961	0.48	0.10	327	0.53	298	0.48	0.09
Psychiatric disorders	220	0.34	1,336	0.33	0.04	207	0.34	190	0.31	0.06
Medications prior to cohort entry										
Antidiabetic agents	21	0.03	109	0.03	0.04	21	0.03	13	0.02	0.08
Statins	22	0.03	80	0.02	0.09	21	0.03	12	0.02	0.09
ART adherence (MPR (mean,SD))	92	21.0	87	25.7	-0.20	91	22.5	89	24.5	-0.09
Requiring prophylactic antibiotics	177	0.28	1,505	0.37	-0.19	176	0.29	181	0.29	-0.02
ART initiation (Year of cohort entry)										
2008	27	0.04	374	0.09	-0.20	27	0.04	26	0.04	0.01
2009	28	0.04	378	0.09	-0.19	28	0.05	39	0.06	-0.08
2010	35	0.05	332	0.08	-0.10	34	0.06	29	0.05	0.04
2011	60	0.09	340	0.08	0.04	60	0.10	60	0.10	0.00
2012	65	0.10	400	0.10	0.01	65	0.11	62	0.10	0.02
2013	51	0.08	508	0.12	-0.15	51	0.08	52	0.08	-0.01

2014	30	0.05	679	0.17	-0.39	30	0.05	30	0.05	0.00
2015	42	0.07	671	0.16	-0.31	42	0.07	36	0.06	0.04
2016	301	0.47	414	0.10	0.90	280	0.45	283	0.46	-0.01
Type of medical institution										
Tertiary hospitals	399	0.62	2,802	0.68	-0.13	397	0.64	405	0.66	-0.03
Others	240	0.38	1,294	0.32	0.13	220	0.36	212	0.34	0.03
Region of medical institution										
Metropolitan cities	504	0.79	3,103	0.76	0.07	482	0.78	501	0.81	-0.08
Rural	135	0.21	993	0.24	-0.07	135	0.22	116	0.19	0.08
Health Insurance status										
National health insurance	593	0.93	3,829	0.93	-0.03	571	0.93	581	0.94	-0.07
Medical aid	46	0.07	267	0.07	0.03	46	0.07	36	0.06	0.07
Ever received NRTI of known CVD risk[a]	28	0.04	1,235	0.30	-0.73	28	0.05	29	0.05	-0.01
Ever received PI of known CVD risk[b]	139	0.22	1,413	0.34	-0.29	138	0.22	125	0.20	0.05

AIDS, acquired immuno-deficiency syndrome; ART, antiretroviral treatment; COPD, chronic obstructive pulmonary disease; MPR, medication possession ratio;

[a] Didanosine, stavudine, and zidovudine

[b] Lopinavir, indinavir, and darunavir including ritonavir boosted products

Table 6. Hypertension Risk of Abacavir Compared to Non-Abacavir ART among HIV-Infected Individuals without Switch

	Before matching			After matching		
	HR	95% CI	p	HR	95% CI	p
Overall	1.1	0.8-1.3	0.6	1.7	1.0-3.0	0.06
Gender						
Women	1(ref)			1(ref)		
Men	1	0.7-1.4	0.9	1.5	0.6-3.8	0.4
Age						
<30	1(ref)			1(ref)		
30≤	2	1.6-2.6	<0.0001	2.3	1.4-3.1	0.05
Type of medical institution						
Tirtiary hospital	1(ref)			1(ref)		
Others	1	0.9-1.3	0.6	1.2	0.8-1.8	0.5
Region of medical institution						
Seoul (capital city)	1(ref)			1(ref)		
Metropolitan cities	1.2	0.9-1.4	0.2	1.1	0.7-1.8	0.7
Rural	1.1	0.9-1.4	0.4	1.4	0.8-2.3	0.3
Health Insurance status						
National health insurance	1(ref)			1(ref)		
Medical aid	1	0.7-1.3	0.8	0.6	0.3-1.3	0.2
Comorbidity prior to cohort entry						
Acute kidney failure	1	0.6-1.4	0.7	0.6	0.2-1.5	0.3
Alcohol	0.9	0.6-1.3	0.5	1	0.5-2.0	1
Cancer	1.3	1.0-1.8	0.1	1.7	0.9-3.0	0.1
Cardiovascular disease	1.8	1.0-3.0	0.04	1.2	0.4-4.1	0.8
COPD	1.2	0.9-1.5	0.2	1.4	0.9-2.4	0.2

Diabetes mellitus	1	0.7-1.3	0.9	0.7	0.3-1.4	0.3
Dyslipidemia	1.2	0.9-1.4	0.2	1	0.6-1.5	0.9
Hepatitis B infection	1.6	1.2-2.2	0.002	2.3	1	0.1
Hepatitis C infection	0.8	0.5-1.1	0.1	1.2	0.6-2.5	0.5
Osteoporosis	0.7	0.4-1.3	0.2	0.6	0.2-2.1	0.4
Prior hospitalization	0.9	0.7-1.0	0.1	0.9	0.6-1.4	0.6
Psychiatric disorders	1.2	1.0-1.4	0.1	1.8	1.0-2.5	0.06
Medications prior to cohort entry						
Antidiabetic agents	1.6	1.0-2.4	0.04	2.1	0.8-5.4	0.1
Statins	1.9	1.2-3.0	0.005	2	0.7-5.3	0.2
ART adherence (MPR)						
80≤MPR	1(ref)			1(ref)		
MPR < 80	1.2	1.0-1.4	0.1	1.7	0.8-2.6	0.2
AIDS defining illness	1.02	0.8-1.2	1	1.1	0.6-1.7	0.8
Requiring prophylactic antibiotics	1.28	1.1-1.5	0.002	1	0.6-1.5	0.9
ART initiation (Year of cohort entry)						
< 2013	1(ref)			1(ref)		
2013≤	1.6	1.2-2.1	0.003	2.9	1.1-3.0	0.05
Ever received NRTI of known CVD risk[a]	0.7	0.6-0.9	0.01	1	0.5-2.0	1
Ever received PI of known CVD risk[b]	1	0.8-1.2	1	1.3	0.8-1.9	0.3

AIDS, acquired immuno-deficiency syndrome; ART, antiretroviral treatment; COPD, chronic obstructive pulmonary disease; MPR, medication possession ratio;

[a] Didanosine, stavudine, and zidovudine

[b] Lopinavir, indinavir, and darunavir including ritonavir boosted products

Table 7. Hypertension Risk of Abacavir Compared to Non-Abacavir ART among HIV-Infected Individuals without Switch Stratified by the Year of Diagnosis

	< 2013			2013≤		
	HR	95% CI	p	HR	95% CI	p
Overall	1.0	0.4-2.3	0.9	3.1	1.3-7.2	0.01
ART adherence (MPR)						
80 ≤ MPR	1(ref)			1(ref)		
MPR < 80	1.5	0.4-5.1	0.5	2.3	0.9-3.1	0.07
Age						
<30	1(ref)			1(ref)		
30≤	3.8	1.2-11.7	0.02	2.1	1.1-4.2	0.04
Comorbidity prior to cohort entry						
Cancer				2.5	1.2-5.2	0.01
COPD				1.9	1.0-3.5	0.05
Psychiatric disorders				1.9	1.2-3.1	0.01
Medications prior to cohort entry						
Antidiabetic agents				3.8	1.2-11.5	0.02

COPD, chronic obstructive pulmonary disease; MPR, medication possession ratio

4. Discussion

The number of HIV-infected individuals detected from the HIRA claims database was similar with that of the government reports. The higher numbers of incident patients of the claims cohort reflects the clinical trend of receiving ART as early as one is diagnosed in recent days.

In this nationwide cohort of incident HIV-infected individuals on initial ART from 2008 to 2016, the incidence rates of hypertension were 4.6 per 100 PY among abacavir users and 3.6 per 100 PY for non-abacavir users. User of abacavir showed a higher risk of hypertension than non-abacavir ART users only in some subgroups. The incidence rate of hypertension from this study is comparable with the 4.6 per 100 PY reported among the general population, calculated from a study in the ROK.[21] The incidence rate of hypertension among ART users from this study may be interpreted as higher than the general population because the cohort of HIV-infected individuals was a much younger group of people; individuals aged ≥50 years made up only 16% of the cohort, compared to 53% among the general population in 2017. However, the incidence rate in this study was higher than those from North American cohorts: 2.6 per 100 PY overall, 2.2 per 100 PY for non-Blacks, and 3.3 per 100 PY for Blacks among HIV-infected individuals on ART15 and 3.4 per 100 PY among heterogeneous PLWH including about 59% of Blacks and 90% on ART.[22] Racial disparities in the occurrence of hypertension among PLWH was shown in other studies,[15,22] as well as among the general population.[23]

Even though the main analysis of the CPH model revealed a similar risk factors as found in other studies such as old age[24,25] and being male[25], the higher risk among the poor adherence group questioned the validity of the model. Those with a more strict definition of which were HIV-infected individuals without any switch revealed a more interpretable results on the risk

of abacavir. Even though, propensity score matching thereafter decreased the number of subjects from 6093 to 1234, the results seemed to be more explainable. Therefore, not only there was a bias toward the null hypothesis resulting from the switch between the exposure and reference group, but also the validity of the CPH model could have been affected.

Among those after matching, abacavir elavated the risk of hypertension with a marginal significance, and those aged same or over 30's, those with psychiatric disease history, and those diagnosed with HIV infection after the year 2013 were risk factors in this association. However, when stratified by the year of diagnosis, recently diagnosed individuals had higher adherence (80≤ MPR 93.0% vs 77.2%), higher proportion of aged<30 (43.2% vs 25.3%), and higher proportion of those with psychiatric disease history (34.1% vs 28.6%). These people who often visited clinics for ART could have been diagnosed with hypertension more than the control group (detection bias). Also, since there were reports such as NEJM Journal Watch giving alert about CVD risk of abacavir, which continued until recently, those prescribed with abacavir could have been monitored with blood pressure more often than the control group (differential ascertainment detection bias). However, while the risk of abacavir is assumed to be based on inflammation, since those with good adherence must have less effect of inflammation rooting from HIV infection itself, the risk of abacavir found among those with good adherence might not be explained only by biases. Therefore, those with good adherence should be monitored with blood pressure when prescribed with abacavir.

PAF was calculated in this study and was 12%. This indicates that, among a variety of risk factors affecting hypertension, about 12% of incident cases occurred as the result of abacavir in HIV-infected individuals on ART. The size of the PAF is comparable with the PAFs for diabetes or high cholesterol (both, 13%) in the USA.[26]

Sensitivity analyses were done by the definition of outcome and the study subjects. Up to now, the biological mechanism of abacavir effect on hypertension (or CVD) is still unknown. After exploring the pattern of outcomes, we assumed that increase in blood pressure must take a constant slope of appearance. Actually, in case of CVD risk of abacavir, the issue in many of the studies was 'when' the risk became maximized. While some studies only reported recent (within 6 months) exposure as being a risk,[4,14,37] other studies reported this risk to be high after 3 years,[33,38] and in another study, the risk peaked after 13-24 months of exposure.[32] However, in case of hypertension we expected hypertension as a steady progress of physiologic change.

This study has strengths in its study design. First, it used approaches to take into account for immortal time bias[36]: time-dependent definition for the drug exposure and initial ART use requirement for the study population. This study treated drug exposure as a time-varying covariate measured in a daily unit to precisely reflect exposure, and it included incident HIV-infected individuals who were all starting their initial ART from a nationwide cohort, which provides high homogeneity and decreases survival bias. Second, we decided to evaluate the risk of long term exposure of hypertension risk to reflect current situations in the real world where PLWH are not being recommended to change abacavir after a certain period of use. Therefore, PLWH on abacavir for many years were our main interest to ensure that the results can be generalized to those on abacavir for as long as 9 years. It was suggested that the duration of ART treatment may modify the association between ART and hypertension among PLWH.[3] In addition, the study period was as long as 9 years and included the era of new combination ART agents in the market. In ROK, tenofovir/ emtricitabine/ elvitegravir/ cobicistat (TDF/ FTC/ EVG/ c) was released in 2014 and abacavir/ lamivudine/ dolutegravir (ABC/ 3TC/ DTG) in 2015. Third, in seeking causal inference concerning the

detrimental effect of abacavir, confounding by indication and channeling bias is particularly important, because switching of drugs is common. For example, the alternate treatment of choice for abacavir, tenofovir, is avoided in patients with poor renal conditions[39]; after the 2008 D:A:D publication, abacavir was avoided in patients with CVD risk.[34] During the study period, patients who received abacavir as their initial ART were 897 (13.8%), and 2056 (31.7%) had changed ART between abacavir and non-abacavir ART with a maximum of 21 switching times. Therefore, we included a number of potential confounders that may affect treatment choice or outcomes. Potential confounders were defined based on the information before cohort entry in order to overcome reverse causation. In case of comorbidities, not only the primary diagnosis but all the other reasons for clinical visits were included.

Our study has several limitations including the use of administrative database without information on smoking status or glomerular filtration rate (GFR). However, GFR did not seem to influence the association between abacavir exposure and CVD risk in a previous study[14]. However, we included the history of acute kidney failure and ESRD prior to cohort entry in order to adjust for renal function and chronic obstructive pulmonary disease in order to adjust for smoking status using diagnostic codes that were strictly supervised by the government for reimbursement. Also, in selecting the study population, an arbitrary time of one year was used to identify incident PLWH on initial ART. Therefore, some HIV-infected individuals who never visited any medical institution could have been excluded. However, the number of yearly incident HIV-infected individuals selected in our cohort was similar to the number reported in an official government report.[40] In addition, in order to evaluate the potential population impact using PAF, there should be a causal relationship between the exposure and the outcome. However, as of yet, the mechanism between abacavir and hypertension remains unclear. Also, abacavir is not such an exposure that could be eliminated for the entire exposure

group. Nevertheless, PAF enabled the evaluation of the quantitative risk of abacavir.

5. Conclusion

In conclusion, the similar numbers between the KCDC reports and this cohort constructed from the HIRA claims database highly suggests the possibility of further application of this database, while there is no such data regarding HIV-infected individuals in Korea. Considering a PAF of 12%, abacavir use should be followed by regular monitoring on blood pressure, especially among those with good ART adherence. Even though this study could not show a concrete result on the risk of hypertension of abacavir due to lack of statistical power, we showed the importance in arbitrary definitions of outcome and the different risk of abacavir between the groups by the year of diagnosis.

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국문초록

배경 : 항레트로바이러스제(ART)인 아바카비어는 심혈관계질환의 발생위험과 연관성이 제기된 바 있으나 고혈압과의 연관성은 연구된 적이 없다.
목적 : HIV 감염인 연구를 건강보험청구자료를 활용하여 수행하며, 감염인의 고혈압 발생률과 아바카바이어로 인한 고혈압 발생위험을 평가한다.
방법 : 2007-2016년 국민건강심사평가원의 청구자료를 이용하여 HIV 감염자 코호트를 구축하였다. 전 국민 코호트에서 6,493명의 코호트 입적 당시 고혈압이 없었던 신규 감염된 HIV감염자를 대상으로 고혈압의 발생률을 추정하고, 이를 통해 Population attributable fraction(PAF)을 산출하였다. 이 연구대상 전체와 노출군과 대조군 간 약물 변경이 없는 감염인만 대상으로 제한한 후 propensity score (PS) matching을 한 1,234명을 대상으로 Cox proportional hazard model을 이용하여 abacavir 약제로 인한 고혈압 발생위험을 교란변수를 보정한 hazard ratio(HR)와 95%신뢰구간(CI)을 산출하였다. ART 처방은 하루 단위의 time-varying covariate로 적용하여 시간에 따라 처방여부가 변하는 것을 반영하였다.
결과: 청구자료를 이용한 HIV 감염인 코호트는 질병관리본부에 신고된 감염인 숫자와 크게 다르지 않았다. 아바카비어 처방자와 비처방자(다른 ART 처방자)의 고혈압 발생률은 각각 100인년 당 4.6과 3.6이었고, 이로부터 PAF은 12로 산출되었다. 약제변경없는군 내에서 PS matching된 대상에서 아바카비어 노출은 고혈압 발생의 위험을 높이는 것으로 나타났으나 통계적으로 경계성 유의성을 보였다(HR 1.7 [95%CI, 1.0-3.0], P value, 0.06). 이 연관성에 30대 이상의 연령, 정신과 질환의 병력, 2013년 이후 진단 이력은 유의하게 영향을 미치는 인자로 나타났다.
결론 : 건강보험청구자료를 이용하여 HIV 감염인에 대한 역학연구가 가능한 자료원 구축을 통해 향후 이 자료원의 활용가치가 크다. 아바카비어 약제 처방 시 혈압에 대한 모니터링이 필요하며, ART 순응도가 높은 최근 진단자에서 특히 그러하다.
주요어 : 고혈압; 아바카비어; 인간면역결핍바이러스; 레트로바이러스제; 약물역학
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